**REMARKS:**

Claims 12-17 are in the case and presented for consideration.

Claim 12 has been amended to clarify the scope of the presently-claimed invention. Specifically, claim 12 has been amended to highlight that the carrier is "plastic viscous." Support for this amendment may be found at least at paragraphs [007], [0021], and [0022] of the published application.

**Rejections Under 35 U.S.C. §103(a)**

The Office maintains its rejection under 35 U.S.C. §103(a) of claim 12 as being unpatentable over the publication in the *International Journal of Pharmaceutics* 144 (1996) 107-114) by Hampl et al. ("Hampl et al.") in view of U.S. Patent Publication No. 20040057970 by Domb ("Domb").

The Office asserts that Domb teaches a "liquid polymeric implant, made of biodegradable polymer matrix loaded with an anticancer agent. The effective anticancer agent, Cisplatin or Paclitaxel, is homogeneously dispersed into the polymer matrix. The active drug is released in a controlled manner to the surrounding tissue, when placed in contact with body fluids, while the polymer carrier is eliminating itself by slow degradation. The implant in a form of ... liquid polymer ... or injectable microspheres is injected into the tumor ... The implant is providing a high dose of anti-cancer drug for an extended period of time, in the tumor site, with minimal systemic drug distribution, thus, providing a localized treatment of the residual tumor cells as a complementary drug therapy to the surgery." Office action at p. 3, citing Domb at par [0046].

The Office concedes, however, that Domb does not expressly teach the anticancer agent distributed in a biodegradable oligoester carrier prepared by a polycondensation

reaction. *Id.*

It is stated in the Office action that this teaching is supplied by Hampl et al. which, it is asserted, teaches oligoesters, specifically, a terpolymer (GA-M-DLLA) of DL-lactic acid (LA), glycolic acid (GA) and mannitol (MA), a copolymer DL-lactic acid and mannitol (M-DLLA) and lactide-glycolide copolymers (DL-PLGA). The GA-MDLLA was prepared by the polycondensation reactionof LA (45.05 mol), GA (45.06 mol) and MA (0.9 mol) and has a Tg of 20°C, Mn of 2.20Kda and Mw of 3.95 kDa. Bovine serum albumin (BSA) was the active ingredient entrapped in microspheres prepared with the terpolymer of GA-M-DLLA which depicted prolonged release of BSA over 15 weeks. The Office also notes that the microspheres were administered subcutaneously to mice. *Id.* at pp. 3, 4.

The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a liquid polymeric implant comprising an anticancer agent homogeneously dispersed into a biodegradable polymer matrix, as taught by Domb and to substitute the polymer matrix of Domb with the terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction) that allows prolonged release of a biodegradable composition, as suggested by Hampl et al., in order to arrive at the instant invention. *Id.* at p. 4

It is reasoned that one of ordinary skill in the art would have been motivated to do this because Hampl et al. teaches that terpolymer of GA-M-DLLA allows the prolonged release of the active ingredient over 15 weeks. The conclusion is that it would have been obvious to substitute the biodegradable polymer matrix of Domb with the biodegradable polymer matrix of Domb because both matrices allow controlled release of the active ingredient. *Id.*

In the Office's view, the teachings of the references make it is apparent that one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is held to have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references. *Id.* at pp. 4, 5.

Turning specifically to claim 12, the Office views the biodegradable composition with prolonged release to have been obvious over the biodegradable composition with prolonged release taught by Hampl et al. It is asserted that the limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl et al. It is asserted that this oligoester composition would intrinsically have the plastic viscous attributes as instantly claimed. The limitation of the antitumor composition and the antitumor agent is deemed to have been obvious over the antitumor composition comprising anti-cancer agents (Cisplatin and Paclitaxel) that are homogeneously distributed in the polymer matrix, as taught by Domb. The limitation of the "antitumor agent for administration into tissues" is deemed to have been obvious over the antitumor composition comprising Cisplatin and Paclitaxel that is injected into the tumor, as taught by Domb, in view of the subcutaneous administration of the composition to mice, as taught by Hampl et al. The limitation of the biodegradable oligoester is considered to be obvious over the terpolymer (GA-M-DLLA) taught by Hampl et al. The limitation of the Mn from 650 to 7,500, the Mw from 800 to 10,000, and the Tg from -35 to 45°C, is also held to be obvious over the Mn of 2.20Kda, Mw of 3.95 kDa, and Tg of 20°C, as taught by Hampl et al. It is also asserted that the limitation of the polycondensation reaction would also have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl et al. The Office also views the limitation of the polyhydric alcohol containing at least 3 hydroxy groups as obvious over the mannitol in the oligoester

taught by Hampl et al. Further, it is asserted that the limitation of the aliphatic a-hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl et al. The Office also considers the molar ratio of the polyhydric alcohol to aliphatic a-hydroxy acid to have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl et al. The limitation of the form of the composition as a homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion is also considered have been obvious over the liquid polymer implant taught by Domb. *Id.* pp. 5, 6.

The Office rejects the position that Hampl et al. fails to disclose a "biodegradable oligoester" as claimed in claim 12 and that the oligoesters of the present invention are structurally different from Hampl et al.'s co- and terpolymers. *Id.* p. 9.

In the Office's view, Hampl et al. teaches a biodegradable oligoester composition with prolonged release. The limitation of the biodegradable oligoester would have been obvious, it is stated, over the terpolymer (GA-MDLLA) taught by Hampl et al. The limitation of the Mn from 650 to 7,500, the Mw from 800 to 10,000, and the Tg from -35 to 45°C, is also held to be obvious over the Mn of 2.20Kda, Mw of 3.95 kDa, and Tg of 20°C, as taught by Hampl et al. The Office notes that the limitation of the polycondensation reaction would have been obvious over the GAM-DLLA that was prepared by polycondensation reaction, as taught by Hampl et al. The Office asserts that the limitation of the polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl et al. The limitation of the aliphatic a-hydroxy acid is deemed obvious over the DL-lactic acid in the oligoester taught by Hampl et al. The molar ratio of the polyhydric alcohol to aliphatic a-hydroxy acid is deemed obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl et al. Based on these findings,

all the limitations of the biodegradable prolonged release oligoester composition of instant claim 12 were held obviated by the teachings of Hampl et al. In the Office's view, one of ordinary skill in the art would find it obvious to modify conditions (temperature, pressure, reaction time) of the polycondensation reaction based on the guidance of Hampl et al., during the process of routine experimentation, since these are manipulatable conditions. *Id.* at pp. 10.

The Office also notes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all optimum and operable conditions (e.g. temperature, pressure, reaction time), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. *Id.* at pp. 10, 11.

The Office also does not agree that Hampl et al.'s co- and terpolymers cannot be administered, under normal temperature and pressure conditions, in a plastic state. It is reasoned that the limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl et al. This oligoester composition would, the Office maintains, intrinsically have the claimed plastic viscous attributes. *Id.* at p. 11.

The Office rejects the argument that Hampl et al. resorts to a releasing system based on microspheres which is notoriously different from that based on the *in situ* implant in form of a viscous liquid as used in the presently-claimed invention. It is noted that Domb teaches a liquid polymeric implant and that the combination of the liquid polymeric implant with the plastic oligoester composition (with the Tg of 20°C) obviates the plastic, viscous composition as in the presently-claimed composition. *Id.*

Further, the Office is not persuaded that the oligoesters of the present invention

have a relatively low sensitivity to changes in pH of the physiological medium into which the antitumor agent is to be released and that, by contrast, the polyanhydrides disclosed in Domb are known to be very sensitive to changes in pH. The Office deems the oligoester limitation to be obviated by the teaching of Hampl et al. (with the relative molecular mass, mean relative molecular mass, glass transition temperature). *Id.* at p. 12.

The rejection is duly noted, but Applicants respectfully traverse.

The Office largely bases its holding of the obviousness of presently-claimed antitumor composition on the assumption that the claimed oligoester could have been obviously identified from Hampl et al. as a suitable carrier for the invention composition. Specifically, the Office action states, "the limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl et al. This oligoester composition will intrinsically have the plastic viscous attributes as instantly claimed" *Id.* at p. 11

The Applicants respectfully disagree with this interpretation of the content of Hampl et al. Hampl et al. describes, in fact, only two specific ter(co)polymers having mannitol as bridge component, i.e. terpolymer of DL-lactic acid, glykolic acid and mannitol (GA-M-DLLA) and copolymer of DL-lactic acid and mannitol (M-DLLA). Both ter(co)polymers are evidently non-plastic/viscous under normal temperature and pressure conditions. Even though this non-plastic/viscous character of both ter(co)polymers is not expressly mentioned in Hampl et al., this non-plastic/viscous character of both Hampl et al.'s ter(co)polymers follows from the fact that their only their use - as mentioned by Hampl et al. - is to form a microcapsule shell. This use clearly excludes the possibility of a plastic/viscous character of Hampl et al.'s ter(co)polymer. In addition, nowhere in Hampl

et al. is there any mention or hint of oligoesters based on DL-lactic acid, glykolic acid and mannitol having the plastic/viscous character. The only reasonable conclusion of this is that Hampl et al. neither mentions nor suggests the oligoesters based on DL-lactic acid, glykolic acid and mannitol being plastic viscous under normal temperature and pressure conditions. This conclusion contravenes the affirmation that Hampl et al.'s composition would intrinsically have the claimed plastic attribute since it is not likely that a non-plastic/viscous composition has the same attributes of a plastic/viscous composition.

In contrast to Hampl et al., the presently-claimed composition takes advantage of a wide range of plastic/viscous oligoesters based on polyhydric alcohols and α-hydroxy acids having values of Mn, Mw and Tg of the ranges defined, respectively, in claim 12. The fact that the specific values of Mn, Mw and Tg for the Hampl et al.'s non-plastic/viscous ter(co)polymer as provided in Table 1 of Hampl et al. fall into the respective ranges of the present claim 12 is not particularly relevant since the plastic/viscous oligoesters of the presently-claimed invention are additionally delimited by the fact that they must be plastic/viscous. This additional obligatory condition inherently excludes the Hampl et al.'s non-plastic/viscous ter(co)polymers from the definition of the present claim 12. Even though the plastic/viscous consistency of the oligoesters used in the presently-claimed invention inherently follows from the plastic/viscous consistency of the claimed composition (the plastic/viscous consistency of the claimed composition is clearly provided by the oligoester carrier itself rather than by the antitumor agent), the Applicants have emphasized this reality by highlighting that the carrier is "plastic viscous." The structural difference between the Hampl et al.'s ter(co)polymers and those of the presently-claimed invention (which difference simultaneously conditions the substantially solid and plastic/viscous state of both types of oligoesters) is based on the fact that the oligoesters

of the presently-claimed invention have a higher branching degree g' as noted in Applicants' reply to the previous official action.

Based on the above explanation of the content of Hampl et al.'s teaching, it is clear that the subject-matter of present claim 12 can by no means be obviated by Hampl et al. One of ordinary skill in the art aspiring to prepare a biodegradable plastic viscous antitumor composition, intended for administration at plastic viscous state into tissues by a syringe with tubing, trocar needle or other needle of a suitable size (cf. paragraph [0022] of the published application) to obtain an *in-situ* implant in the form of a viscous liquid, would not have been motivated at all to do so by Hampl et al. This is because Hampl et al. only taught non-plastic/viscous oligoesters which are, as carriers, absolutely unadaptable for the plastic viscous composition presently called for and which were used by Hampl et al. to form non-liquid microcapsule shells.

Hampl et al. also would not have suggested to a person of ordinary skill in the art whether some other oligoesters of plastic/viscous character could have been derived from those described in Hampl et al. since Hampl et al. is absolutely silent on this point. Even though the person skilled in the art may have modified the Hampl et al.'s preparative conditions in order to try to prepare some plastic/viscous oligoesters of Hampl et al.'s kind, he could not have a reasonable expectation of success in the absence of any suggestion from Hampl et al.

Nor was it obviously detectable from Hampl et al. that the preferred release regime promoted by the acid degradation products further catalyze the degradation of the presently-claimed invention's plastic viscous composition. Hampl et al. does not at all mention this catalysis mechanism. Further, this catalysis mechanism only proceeds to an exploitable extent in a bigger system.

Based on the foregoing, Applicants respectfully submit that Hampl et al. does not supply the above-referenced teachings, nor are these teachings supplied by Domb.

Further, the presently-claimed composition is not obvious in view of the combination of Hampl et al. and Domb, since if the Domb' s polyanhydride viscous polymer matrix is replaced with Hampl et al.s's non-viscous ter(co)polymer matrix, no viscous composition is obtained. Thus, the combination Hampl et al. and Domb would not have lead a person of ordinary skill in the art to the claimed composition.

In addition, the preferred release regime promoted by the fact that the acid degradation products further catalyze the degradation of the invention composition was not obviously detectable from Domb since the degradation of Domb' s composition takes place under a quite different chemical mechanism.

Therefore, it is respectfully submitted that because both Hampl et al. and Domb either fail to disclose critical claimed elements or teach away from using the critical elements of currently amended independent claim 12, from which all other claims depend, and because neither reference provides a teaching which would lead one of ordinary skill in the art to arrive at the presently-claimed invention, the combination of Hampl et al. and Domb does not render any of the present claims obvious.

The Office has also maintained its rejection under 35 U.S.C. §103(a) of claims 13-17 as being unpatentable over Hampl et al. in view of Domb and further in view of U.S. Patent No. 5,783,205 to Berggren et al. ("Berggren et al.").

The rejection is also duly noted but Applicants respectfully traverse.

As noted above, both Hampl et al. and Domb both individually and in combination

fail to disclose or suggest critical elements claimed in currently amended independent claim 12, from which all other claims depend. These elements are not supplied by Berggren et al. Furthermore, as is the case with Hampl et al. and Domb, Berggren et al. fails to provide a teaching or suggestion which would be sufficient to motivate one of ordinary skill in the art to arrive at the otherwise missing elements. Further, it is well-settled that dependent claims contain all the elements of the claims from which they depend.

Therefore, because the above-cited prior art references either fail to disclose critical claimed elements and/or teach away from the presently-claimed combination, and because the aforementioned references also fail to provide a teaching, suggestion or motivation which would cause one of ordinary skill in the art to arrive at the presently-claimed invention, none of the current claims are obvious in light Hampl et al., Domb and Berggren et al., both individually and in combination.

**Conclusion**

Accordingly, Applicants believe that all the claims are now in condition for allowance and favorable action is respectfully requested. Should there be any issues that have not been addressed to the Examiner's satisfaction, Applicants invite the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, please charge such fees to Deposit Account No. 14-1431.

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